UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOHN F. CONROY, MARY E. POWER, and PAMELA M. NORRIS

Appeal 2006-3259
Application 09/785,188
Technology Center 1600

ON BRIEF

Before GRIMES, GREEN, and LINCK, *Administrative Patent Judges*.

LINCK, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants appeal the Examiner's § 103(a) rejections of claims 15-26, 28, 29 and 31-39, all pending claims in the above-identified application, filed February 20, 2001. We have jurisdiction to decide this appeal under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

The Specification

The claimed invention generally relates to sol-gel-derived materials and is more specifically "directed toward . . . the formation of robust, macroporous samples" and the samples so formed. Specification ("Spec.") at 1. According to the specification, "sol-gel-derived materials" have "several favorable characteristics . . . as immobilization matrices, including . . . low temperature production routes, chemical-, temperature-, and radiation stability, high surface area and porosity, ease of functionalization, mechanical rigidity (little or no swelling), and tunable properties and microstructure." *Id.*

Further according to the specification, despite "the promise of sol-gel-derived materials, limited progress in the use of sol-gel-derived materials as a cell immobilization matrix has been made." *Id.* at 2. "Common sol-gel production methods are too cytotoxic at the time of gelation for extensive use in the immobilization of cells. Furthermore, macroporous samples amenable to colonization are difficult to obtain and may require the use of toxic chemicals." *Id.* The stated reasons for these prior art difficulties appear to be found in problems with the sol's production. *Id.* at 2-3.

Appellants provide:

> [A] method and a sol that can be used to form gels that are compatible with biological materials and/or robust and macroporous. As needed, the two step nature of the gelation reaction can be exploited to allow removal of undesired organic solvents such as hydrolysis reaction by-products from an acidic aqueous sol prior to gelation. Thus, sols that are substantially free of organic solvents and compatible with biological materials can be produced. Also as needed, robust,

> macroporous gels can be made by introducing water-soluble organic polymers to similar sols, with or without biological materials present [Spec. at 4].

One method according to Appellants' invention includes "hydrolyzing a sol-gel precursor in water to form a sol containing an organic solvent; removing said organic solvent from said hydrolyzed sol; and mixing said biological material with said hydrolyzed sol after said removing step." *Id.* Another includes "hydrolyzing a sol-gel precursor in water to form a sol containing an organic solvent" and "mixing said biological material with said sol" without mention of removal of the organic solvent. *Id.* at 4-5.

The Rejected Claims

Claims 15-26, 28, 29 and 31-39 are pending and have been rejected under 35 U.S.C. § 103(a) based on various combinations of the following references:

Hino et al. U.S. 4,148,689 Apr. 10, 1979

Uo et al., "Immobilization of Yeast Cells in Porous Silica Carrier with Sol-Gel Process," Journal of the Ceramic Society of Japan, Vol. 100, No. 4 (1992), pp. 426-429.

Klein et al., "Effect of Water on Acid- and Base-Catalyzed Hydrolysis of Tetraethylorthosilicate (TEOS)," Better Ceramics Through Chemistry, Vol. 32 (1984), pp. 33-39.

Rao et al., "Influence of Molar Ratios of Precursor, Catalyst, Solvent and Water on Monolithicity and Physical Properties of TMOS Silica Aerogels," Journal of Sol-Gel Science and Technology, Vol. 3 (1994), pp. 205-217.

Schmidt et al., "Principles of Hydrolysis and Condensation Reaction of Alkoxysilanes," Journal of Non-Crystalline Solids, Vol. 63 (1984), pp. 1-11.

Claims 26, 28, 29, and 31-36 are rejected over Uo and Hino. Claims 15-23, 25, and 37-39 are rejected over Uo, Hino, Kline and Rao. Claim 24 is rejected over Uo, Hino, Kline, Rao, and Schmidt. Examiner's Answer ("Answer") 4, 7 & 8.

Appellants argue claims 26 and 29 together and claims 28 and 15 separately. The remaining claims are not separately argued. *See* Substitute Brief on Appeal ("Br.") 4. Thus, we consider representative claims 26, 28, 15, and 24:

Claim 26. A method, comprising:
mixing a vegetative cell into a sol;
mixing a sufficient amount of a dispersant into said sol to cause macropores in a gel formed by said sol; and
gelling said sol to form said gel.

Claim 28. A gel, comprising:
a macroporous solid network formed by the condensation of hydroxy metallates from a sol solution; and
a bacterial cell added to the sol solution and thereby immobilized within said solid network,
wherein said sol solution is compatible with said bacterial cell.

Claim 15. A sol, comprising:
P moles of a hydroxy metallate;
W moles of water;
a sufficient amount of a dispersant to cause macropores in a gel formed by said sol; and
a biological material,
wherein a ratio of W:P is greater than 25:1.

> Claim 24.[1] The sol [according to claim 15, wherein: said hydroxy metallate is formed by hydrolysis of a sol-gel precursor], further comprising an organic solvent comprising an organic by-product arising from the hydrolysis of said sol-gel precursor.

ISSUE ON APPEAL

Claim 26

The Examiner contends the "method of claim 26 [is] the same as the method . . . disclosed by Uo et al except that the claim[] require[s] a vegetative cell instead of yeast spores." Answer 5. The Examiner further contends Hino cures this deficiency: "It would have been obvious to use vegetative yeast cells in place of the yeast spores in the method of Uo et al as suggested by Hino . . . . Using vegetative cells not in spore form would have been expected to be advantageous due to simplification resulting from not having to convert vegetative cells to spores and then covert the spores to vegetative cells to provide the cells in active form for use." Answer 5-6.

Appellants contend there would have been no motivation to combine Uo and Hino because "one of ordinary skill would expect Uo's gelation solution [containing methanol] to be toxic to Hino's vegetative cells and thus would not have a reasonable expectation of success with the combination." Br. 4. Appellants rely on a "technical understanding of the antimicrobial activity of alcohols" and on Uo's and Hino's teachings for support. Br. 5 (citing DISINFECTION, STERILIZATION, AND PRESERVATION, Ch. 12 ("Alcohols") (Seymour Block ed.) (5th ed. 2001)).

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[1] Claim 24 is dependent upon claim 17; claim 17 is dependent upon claim 15.

Appellants further contend that, to the extent Hino suggests omitting methanol from Uo's method, a "macroporous gel like Uo's without methanol is neither described nor suggested by Uo," particularly since "every recipe for macroporous silica gels in the art of record . . . requires toxic gelation conditions." Reply 5. *See also* Br. 10.

Given these contentions, the single issue before us with respect to claim 26 is, would one of ordinary skill in the art have been motivated to combine the teachings of Uo and Hino to arrive at the method of claim 26?

FINDINGS OF FACT

Interpretation of Claim 26

Claim 26 uses the term "vegetative cell," a term not defined in the specification. We interpret the term to mean a nonreproductive cell, i.e., a cell that is "engaged in nutrition and growth rather than sexual reproduction, and excluding dormant forms." Oxford Dictionary of Biochemistry and Molecular Biology 680 (Oxford University Press 1997).

Claim 26 also uses the term "macropores" without providing a definition in the specification or in the claims. We interpret this term to mean "any pore . . . whose width is greater than about 50 nm." *Id.* at 392.

Claim 26 does not require that the recited "vegetative cells" retain any particular activity level. *See, e.g.*, Answer 6, 11.

Due to "comprising language," claim 26 does not exclude additional components, such as methanol, s*ee id.* at 11, and thus includes a method in which the alcohol is not removed prior to adding the cells. Claim 26. *See also, e.g.*, Spec. at 4; Answer 6.

The method of claim 26 also includes a method in which substantially all alcohol is removed from the sol prior to adding dispersant to cause macropores to form. *See, e.g.*, Spec. at 4, ll. 23-26 & FIG. 1.

The Prior Art Teachings

Uo describes the method of claim 26, except yeast spores rather than the claimed "vegetative cells" are mixed into the sol because "the spores are durable to organic solvents." Uo at 427, ¶ 2.2. *See also* Answer 4-5. Uo includes tetramethyoxysilane (TMOS), water, methanol and polyethylene glycol (PEG) to form the sol. Uo at 426, col. 1; Answer 4.

Uo does not teach that using yeast cells in the disclosed method would kill all activity of the cells but does imply the activity level would be less than when spores are used. *See id.* ¶ 2.2 & *passim*; *see also* Answer 9.

Uo teaches that the pore diameter of the gel is a function of the PEG, water and H_2SO_4 content and is silent on the impact of methanol. Uo at 427, ¶ 3. Thus, there is "inadequate evidence . . . that the methanol of Uo et al is critical to obtaining macropores." Answer 13.

Based on the teachings of Uo and Block (relied upon by Appellants), one skilled in the art would have expected spores to be more stable in the presence of alcohol than cells.

Hino describes the method of claim 26, except Hino (1) does not expressly disclose the formation of macropores in the gel and (2) immobilizes microbial cells instead of spores. Col. 1, ll. 36-37.

One of Hino's objects is "immobilizing microbial cells while maintaining at least more than 50% of the enzymatic activity which was originally shown by the untreated microbial cells." Col. 4, ll. 7-11.

Hino forms the sol "by reacting a water-soluble polymer [e.g., a dispersant such as PEG] and a tetraalkoxysilane" but does not include an alcohol as Uo does. Col. 4, ll. 30-34, 46-62.

Hino's "water-soluble-polymer compound is mixed with the . . . tetraalkoxysilane, and then the pH of the mixture is adjusted below 3 with acid or acidic salt which exhibits no harmful effect on the enzymatic activities of microbial cells." Col. 5, ll. 21-25.

When Hino's hydrolysis of the tetraalkoxysilane is complete, the "original specific smell of tetraalkoxysilane changes to an alcoholic perfume." Col. 6, ll. 6-11.

Hino does not teach that the alcohol formed during hydrolysis should be removed prior to addition of the microbial cells. *See* Hino *passim*.

In spite of the formation of alcohol in the hydrolysis step, according to Hino's teachings, "microbial cells possessing enzymatic activities can be immobilized under quite mild conditions by entrapping them inside the gel matrix . . . produced from the water-soluble-polymer compound and silicate." Col. 6, ll. 53-58.

In one example, Hino's gels were extruded into acetone, methylene chloride and isopropyl alcohol. Col. 15, ll. 63-65. The relative activity was reduced but maintained above Hino's sought-after level, i.e., above 50% (61% for that extruded in isopropyl alcohol). Col. 16, ll. 3-21.

At least two of Hino's gels scatter visible light and thus do not exclude the presence of macropores, as admitted by Appellants. Br. 9-10 (citing Hino, col. 12, l. 6 &35). *See also* Hino, col. 6, ll. 24-25 ("above pH 7, the gel becomes semi-transparent").

The Level of Skill in the Art

The skilled artisan would recognize the value of immobilizing cells by a sol-gel process, as taught by Uo and Hino, and the value of macroporous gels such as those taught by Uo.

Based on the teachings of Hino and Uo (and further in view of those of Block), the skilled artisan would have been aware of the potential toxicity of alcohols to microbial cells. Thus, if necessary to preserve cell activity, the artisan would have minimized contact between the cells and an alcohol, for example, by omitting the addition of alcohol to the reaction mixture when forming the sol, as suggested by Hino. *See* Answer 11.

The skilled artisan would have recognized the value of using "vegetative cells" rather than spores, i.e., to simplify the process. *See* Answer 5-6.

Other Findings

The value of Block's teachings is limited, as it analyzes the impact of alcohols in water rather than in the types of gels relevant to the claimed invention. *See* Answer 11.

DISCUSSION

Based on the above findings, one of ordinary skill in the relevant art would have been motivated to combine the teachings of Uo and Hino to arrive at the method of claim 26. As the Examiner found, such a combination would have involved the substitution of Hino's cells for Uo's spores and, optionally, omitting the methanol from the reaction mixture if necessary to obtain a higher activity level. *See* Answer 5-6, 9-11. The

advantages of immobilizing cells directly rather than their spores would have motivated the skilled artisan to make the substitution. This would have been true, at least in certain circumstances, even believing some activity would be lost. *See* Answer 6-7.

Appellants strenuously argue that there is no suggestion in the prior art that macropores can be formed without methanol present. We disagree. Uo suggests that PEG, water and acid are responsible for their formation, not methanol. In our view, that suggestion is sufficient to support the Examiner's prima facie case of obviousness, a case Appellants have not rebutted with evidence to the contrary. And in that regard, we note Appellants remove their methanol before adding a dispersant to form the macropores.

Claim 28

Claim 28, like claim 26, has been rejected under §103(a) in view of Uo and Hino. Claim 28 differs from claim 26 in that it is to a gel rather than a method and the immobilized cells are bacterial cells. In addition to his findings with respect to claim 26, the Examiner found that "bacterial cells" in claim 28 are not limited to "vegetative cells" and thus include bacterial spores. Answer 13. Thus, according to the Examiner, the skilled artisan would have been motivated to substitute Hino's bacterial cells (in the form of spores) into Uo's method and gel when "a bacterial cell is desired." *Id.* at 14. We agree with these findings.

Appellants respond that there is no teaching of bacterial spores in the references, and Uo "teaches away from exposure of organisms other than robust yeast spores." Br. 12. For the reasons given above, we disagree with

Appellants' reasoning. Further, given that the skilled artisan can use bacterial spores to practice the invention of claim 28, there's even stronger motivation to employ the teachings of Uo. *See* Answer 14. Appellants' remaining arguments with respect to claim 28 mirror those made with respect to claim 26 and have been addressed above.

Claim 15

The Examiner relies on Uo, Hino, Kline and Rao to reject claim 15 under § 103(a). Claim 15 is to a sol comprising P moles of a hydroxy metallate, W moles of water, a dispersant, and a "biological material," which can be yeast spores, "wherein a ratio of W:P is greater than 25:1." The additional disputed limitation with respect to claim 15 is the W:P ratio. Br. 15. The Examiner relies upon Klein, a reference that shows a sol solution with a ratio of 32:1, and Rao, a reference that discloses "the influence ratios of precursor, catalyst, solvent and water [have] on properties of silica aerogels." Answer 7-8, 16.

Appellants respond that a ratio of 32:1 in Klein yields 65% ethanol, an amount Block shows is "effective at killing a number of bacterial species in under one minute." Br. 15-16 (emphasis Appellants'). The Examiner responds that the "biological material" of claim 15 would include the durable yeast spores taught by Uo. Answer 15. Further, according to the Examiner, for the reasons given relating to claim 26, the skilled artisan would have been motivated to reduce the alcohol level, if needed to preserve the activity of the cells. Answer 16. Finally, Block does not disclose the impact of alcohol on cells in a sol-gel process. Answer 11. Thus, the value

of Block's teachings are limited. We agree with the Examiner's findings are reasoning with respect to claim 15.

Claim 24

In addition to the limitations of claim 15, claim 24 requires that the claimed sol contain a hydroxy metallate "formed by hydrolysis of a sol-gel precursor" and an "organic solvent comprising an organic by-product arising from the hydrolysis of said sol-gel precursor." The Examiner rejected claim 24 over Uo, Hino, Kline, Rao, and Schmidt. Schmidt discloses that "hydrolysis of alkoxysilanes produces an alcohol." Final Office Action 8 (mailed 08/24/04). The Appellants do not argue this claim separately. Thus, we rely upon our above analysis to address claim 24.

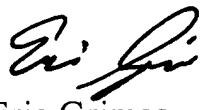
CONCLUSIONS

The Examiner has made a prima facie case that claims 26, 28, 15 and 24 would have been obvious in view of the cited art. Appellants have not successfully rebutted the Examiner's prima facie case. Thus, we affirm the Examiner's rejection of claims 26, 28, 15, and 24.

Lacking any argument regarding their separate patentability, we also affirm the Examiner's rejection of the remaining pending claims 16-23, 25, 29, and 31-39 under 37 C.F.R. § 41.37(c)(1)(vii).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a)(1)(iv) (2004).

AFFIRMED



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